

RESEARCH ARTICLE

How many patients do you need? Investigating trial designs for anti-seizure treatment in acute brain injury patients

Harsh Parikh¹ , Haoqi Sun², Rajesh Amerineni³, Eric S. Rosenthal³ , Alexander Volfovsky^{4,*} , Cynthia Rudin^{4,*}, M. Brandon Westover^{2,*} & Sahar F. Zafar^{3,*}

¹Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

²Department of Neurology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

³Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts, USA

⁴Department of Computer Science, Duke University, Duke, North Carolina, USA

Correspondence

Sahar F. Zafar, Massachusetts General Hospital, Lunder 6 Neurosciences ICU, 55 Fruit Street, Boston, MA 02114, USA.
 Tel: 8572385600; Fax: 8572385601;
 E-mail: sfzafar@mgh.harvard.edu

Received: 21 December 2023; Revised: 19 March 2024; Accepted: 21 March 2024

Annals of Clinical and Translational Neurology 2024; 11(7): 1681–1690

doi: 10.1002/acn3.52059

*Co-senior authors.

This paper has been uploaded to a preprint server <https://www.medrxiv.org/content/10.1101/2023.08.21.23294339v1>.

The manuscript complies with all instructions to authors. The authorship requirements have been met and the final manuscript was approved by all authors. The manuscript has not been published elsewhere and is not under consideration by another journal. The manuscript adheres to ethical guidelines and completed after appropriate IRB approval. The STROBE checklist was used for this study.

Abstract

Background/objectives: Epileptiform activity (EA), including seizures and periodic patterns, worsens outcomes in patients with acute brain injuries (e.g., aneurysmal subarachnoid hemorrhage [aSAH]). Randomized control trials (RCTs) assessing anti-seizure interventions are needed. Due to scant drug efficacy data and ethical reservations with placebo utilization, and complex physiology of acute brain injury, RCTs are lacking or hindered by design constraints. We used a pharmacological model-guided simulator to design and determine the feasibility of RCTs evaluating EA treatment. **Methods:** In a single-center cohort of adults (age >18) with aSAH and EA, we employed a mechanistic pharmacokinetic-pharmacodynamic framework to model treatment response using observational data. We subsequently simulated RCTs for levetiracetam and propofol, each with three treatment arms mirroring clinical practice and an additional placebo arm. Using our framework, we simulated EA trajectories across treatment arms. We predicted discharge modified Rankin Scale as a function of baseline covariates, EA burden, and drug doses using a double machine learning model learned from observational data. Differences in outcomes across arms were used to estimate the required sample size. **Results:** Sample sizes ranged from 500 for levetiracetam 7 mg/kg versus placebo, to >4000 for levetiracetam 15 versus 7 mg/kg to achieve 80% power (5% type I error). For propofol 1 mg/kg/h versus placebo, 1200 participants were needed. Simulations comparing propofol at varying doses did not reach 80% power even at samples >1200. **Conclusions:** Our simulations using drug efficacy show sample sizes are infeasible, even for potentially unethical placebo-control trials. We highlight the strength of simulations with observational data to inform the null hypotheses and propose use of this simulation-based RCT paradigm to assess the feasibility of future trials of anti-seizure treatment in acute brain injury.

Introduction

Up to 50% of patients with acute brain injury undergoing continuous electroencephalography (EEG) exhibit epileptiform activity (EA).^{1–5} EA, characterized by seizures, periodic, and rhythmic patterns, is strongly linked to higher mortality rates and poor functional outcomes in

patients with acute brain injuries (including trauma, ischemic, and hemorrhagic stroke).^{6–9} There is limited data on how EA responds to treatment, and whether treatment improves outcomes.^{6,7} The existing studies examining anti-seizure treatment of EA have major limitations in design and analysis resulting in inconclusive or conflicting findings.^{10–13} The lack of evidence to guide

treatment results in broad anti-seizure treatment, with anti-seizure medications (ASMs) such as levetiracetam or anesthetics such as propofol being commonly prescribed to manage EA.^{4,9–14} The goal of this study is to use observational data to guide trial designs that address the limitations of prior studies and ultimately move the needle toward feasible and practical clinical trials of anti-seizure treatment of EA.

Randomized controlled trials (RCT) are considered the gold-standard approach to assess the effectiveness of clinical treatments and establish evidence-based treatment guidelines.¹⁵ However, conducting RCTs for EEG-guided anti-epileptiform treatment faces challenges stemming from the variability in drug response among patients. Individuals may need different dosage regimens and treatment durations, while clear definitions of treatment targets and endpoints are ill-defined. Moreover, standardizing the timing of EEG initiation and determining the time to randomization can be challenging due to the variable presentation time from ictus. Lastly, randomizing individuals into treatments that are considered likely to be worse than the standard of care is problematic due to ethical considerations. To design a robust trial, it is imperative to meticulously consider these factors.

One of the key aspects of a study design is the determination of a reasonable sample size via a power analysis.¹⁶ Sample size selection in prior RCTs on EEG-guided anti-seizure treatment were not based on realistic power analysis calculations. Limited availability of data on pharmacodynamic heterogeneity and poor-quality data on outcomes resulted in unrealistic null distributions and consequently underestimation of the required sample size.^{13,17} To address these challenges, we propose leveraging observational data in a simulation-aided design of a randomized experiment and power analysis. This simulation-aided approach assists in establishing appropriate sample sizes, optimizing the trial design, and improving the reliability of future estimates.^{18–20}

In this study, we employed mechanistic pharmacological model-guided simulations to assess the feasibility of a trial investigating the effectiveness of anti-seizure medication (ASM) treatment for EA in a subgroup of acute brain injury patients with aneurysmal subarachnoid hemorrhage (aSAH). The target endpoint for these trials was functional outcomes at discharge as measured by the modified Rankin Scale (mRS). Our analysis focuses on evaluating the impact of trial design and drug efficacy in reducing EA burden on the required sample size needed to achieve sufficient statistical power. To accomplish this, we developed a simulator that incorporated real EEG and ASM data from aSAH patients, enabling us to understand and simulate patients' epileptiform activity trajectories during their hospitalization, including the interactions

between EEG and ASM. Using the trained model, we conducted simulated RCTs, varying the ASM doses, to investigate their effects on the modified Rankin Scale.

Methods

We developed a framework to leverage observational data to inform the effect size estimation for the efficient design of experiments in clinically and physiologically complex scenarios (see Fig. 1). Specifically, we studied sequential ASM treatment regimes, where administered treatments not only affect the short-term state (i.e., EEG findings) but also the long-term outcome of a patient (e.g., discharge modified Rankin Score [mRS]), while at the same time capturing patient-level heterogeneity in response to treatment. We designed a simulated randomized control trial that used an estimated mechanistic simulator and long-term effect predictor learned using observational data. The empirical distribution of the pre-treatment covariates is similar to the one in the observational data. This design allowed us to perform power analyses and compare various choices of treatment arms and outcomes.

Patient cohort

The observational study was approved by the Institutional Review Boards of the Massachusetts General Hospital and Duke University. Informed consent was not required. The EEG recordings and clinical and demographic variables were extracted from a retrospective database of adult (age ≥ 18 years) aSAH patients consecutively admitted to Massachusetts General Hospital and underwent cEEG monitoring between 2012 and 2017. Per institutional protocol aSAH patients with Hunt and Hess scores ≥ 3 and Fisher scores ≥ 3 undergo 10 days of cEEG monitoring for ischemia detection. From the initial database of 136 patients with aSAH, we considered a subset of 48 patients who underwent more than 24 h of EEG and had EA during monitoring. We selected this population as all had cEEG initiation at the same time point in their disease course, allowing for homogeneity in the time of EA measurement and treatment interventions. Here, EA was defined as seizures, generalized and lateralized periodic discharges (GPDs and LPDs), and lateralized rhythmic delta activity (LRDA). We included LPDs, GPDs, and LRDA in our definition of EA as all of these are highly associated with seizures and are frequently treated with anti-seizure medications in clinical practice.^{4,6,9,21} In addition, seizures as well as periodic and rhythmic patterns are shown to be associated with similar patterns of metabolic stress.^{22–25} Finally, in clinical practice these patterns are frequently overlapping/not mutually exclusive or on a continuum and isolating to a single pattern would make measuring a response to a treatment trial

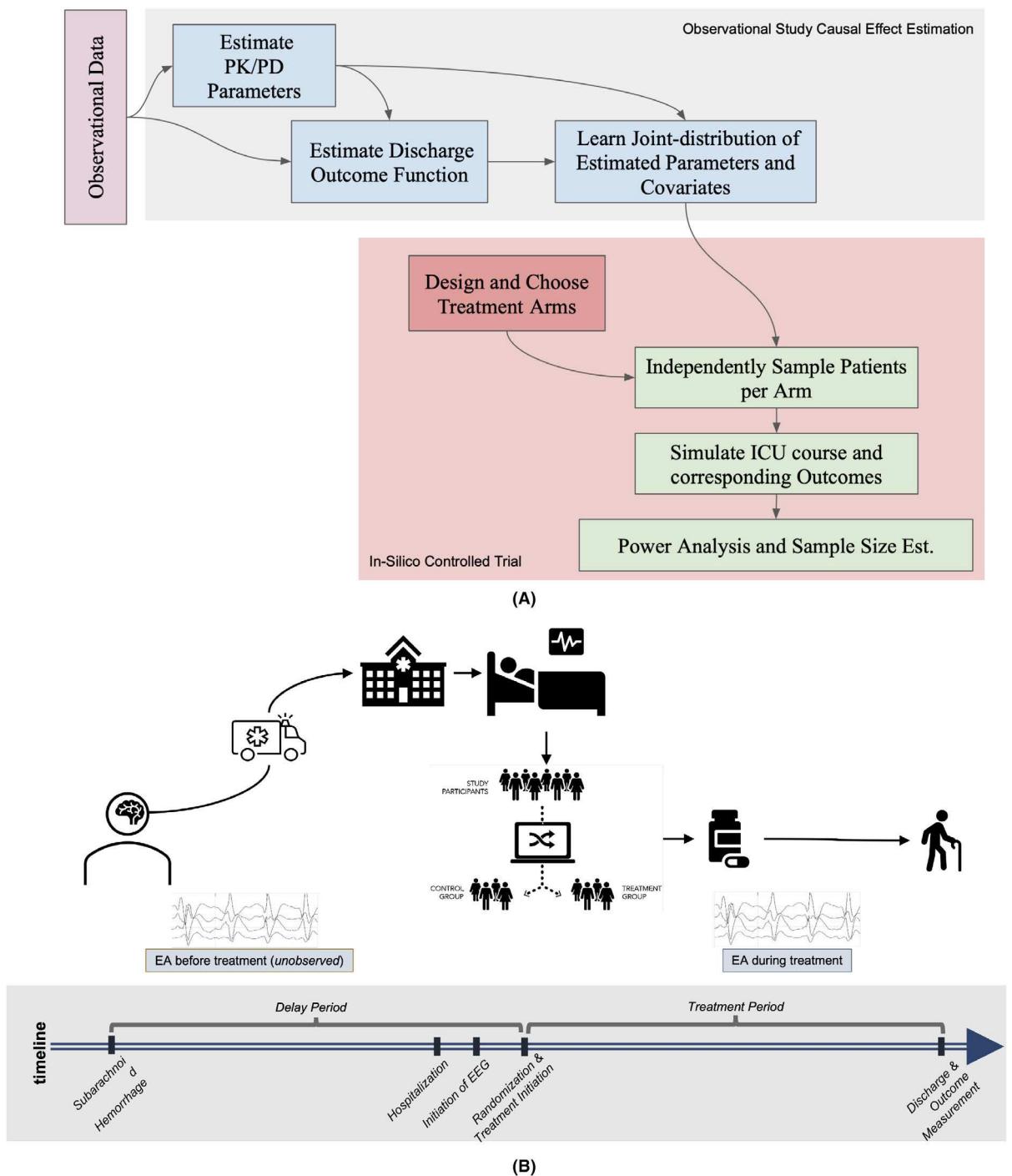


Figure 1. Overall analysis framework and a typical patient's timeline. (A) The analysis framework consists primarily of two parts—estimation using observational data (shown in gray) and simulated RCTs (shown in red). (B) The schematic shows the timeline of a typical patient participating in a prototypical RCT.

more challenging in the present work.^{5,21} Generalized rhythmic delta activity (GRDA) was excluded from our definition of EA as it is a more benign pattern that is not

associated with seizures.⁴ Clinical and demographic variables for the selected patients are shown in Table 1. The median time from admission to EEG initiation was

Table 1. Descriptive table showing the distribution of demographic and clinical covariates.

Variable	Value
Age (median, Q1–Q3)	61 (51–74)
Gender, F (N (%))	38 (79%)
Hunt and hess score	
1	6 (12.5%)
2	6 (12.5%)
3	14 (29.1%)
4	15 (31.3%)
5	7 (14.6%)
Fisher Score	
1	0 (0.0%)
2	2 (4.2%)
3	34 (70.8%)
4	12 (25.0%)
Time to EEG, h (median, Q1–Q3)	24 (24–48)
EEG duration, h (median, Q1–Q3)	183 (139–230)
ASM treatment, N (%)	32 (66.7%)

Note: We provide the percentage of each category for categorical variables and the interquartile range (IQR) for continuous variables.

24 hours. Discharge outcome was measured using the modified Rankin Scale. We dichotomized outcomes as good (mRS < 4) and poor (mRS ≥ 4). The data and software to reproduce these findings are available in a publicly accessible repository at bdsp.io.

EA burden estimation

Increasing EA burden is associated with worse outcomes not only in aSAH patients but also across a wide spectrum of acute brain injury patients.^{6–8} We therefore examined the interaction of EA burden and ASM treatment with outcomes. To measure EA burden in our cohort of aSAH we followed these steps: First, a previously developed convolutional neural network (CNN) classifier was used to label every consecutive 2-sec segment of cEEG data as having one of the EA patterns (seizure, GPD, LPD, LRDA) or not.^{26–28} Then, the EA burden time series was defined as the proportion of 2-sec segments having EA in a moving non-overlapping 10 min window.^{6,7} We used a clinically meaningful summary to quantify EA burden as E_{max} : the maximum EA fraction among 6-h sliding windows. This measure of EA burden was selected based on our prior work demonstrating that the maximum EA burden within a sliding 6-h window has a significant negative effect on discharge neurologic outcome.⁷

Anti-seizure medication and PK/PD modeling

We modeled the short-term effect of ASMs on EA using a mechanistic pharmacokinetics-pharmacodynamics (PK/

PD) model.⁷ PK/PD models are based on biological processes and the parameters have physical or biological interpretation. Estimating PK/PD parameters for each patient allowed us to account for patient heterogeneity across the cohort, which is important in our application. Thus, using mechanistic models guarantees interpretability of the estimates and is well-suited for our application as these models require fewer data to calibrate compared to empirical (nonparametric) statistical models. We used a one-compartment PK model to estimate the concentration of drugs for each patient in the cohort.²⁹ While PK models with more compartments may more accurately capture changes in serum concentration on very short time scales, one-dimensional models sufficed for the treatment time scales of hours considered in the present study, and these simpler models have fewer parameters to estimate. Furthermore, we used Hill's PD model to estimate the short-term effectiveness of the ASMs in reducing the EA burden.³⁰ We estimated the drug concentration necessary to reduce EA burden in a 10-min window by 50% from the maximum level and the steepness of the effect-onset curve (Hill's coefficient), as previously described by our group.^{7,31} We estimated the PK/PD parameters using the observed EA burden and ASM time series from each patient to account for inter-patient heterogeneity. Our estimation method minimizes the mean-squared error between the simulated and observed EA burden trajectories. We delineate the formal mathematical setup of the pharmacological models in Appendix S1.

Discharge outcome modeling

Following our result showing E_{max} in a 6-h sliding window negatively impacts outcomes, with an effect size of 13.5%,⁷ we focused on modeling the outcome (mRS) as a function of E_{max} and average ASM concentration during treatment. We adapted the doubly robust machine learning causal effect estimator³² using gradient boosting trees to learn discharge outcomes as a function of E_{max} and ASMs.⁷ We adjusted for all baseline features (described in Table 1) and their PK/PD parameters as confounders.

Simulated controlled trials

We designed trials to estimate the effectiveness of varying treatment regimens for a commonly prescribed ASM, levetiracetam, and a commonly prescribed anesthetic, propofol. We used the models learned using the observational data (as described in the previous section) to simulate RCTs by generating random samples of patients' EA burden over time (as a function of the ASM treatment regime) as well as discharge outcomes (as a function of

EA burden and ASM exposure). We analyzed how the required sample size and associated power varied with the choice of treatment arms and outcomes defined below. We evaluated the outcome measure of discharge neurologic status measured using the modified Rankin Scale (mRS) dichotomized as good (mRS: 0–3) and poor (mRS: 4–6) outcome.⁷

Treatment arms

For each of the two drugs, we designed three treatment arms based on the drug dose plus standard care and a fourth placebo arm. Our institutional practice is to dose Levetiracetam every 12 h. However, due to additional bolus doses and/or changes in dose timings, the average dosing interval in the observed data was q8 hours. Propofol is dosed as a continuous infusion, with intermittent boluses as needed. For levetiracetam, we used the following three doses (administered every 8 h): (i) 15 mg/kg, (ii) 7 mg/kg, (iii) 3 mg/kg, and (iv) placebo with standard care. Similarly, for propofol, the treatment arms were: (i) 1 mg/kg/h, (ii) 0.5 mg/kg/h, (iii) 0.25 mg/kg/h, and (iv) placebo with standard care. For both drugs, the second treatment dose (7 mg/kg for levetiracetam and 0.6 mg/kg/h for propofol) was chosen based on the median doses used in the observational data. Of the 48 patients with EA, 16 did not receive any anti-seizure treatment, reflecting existing practice variation in ASM prescription for patients with EA.^{4–6,9}

We simulated RCTs with varying sample sizes using our cohort of 48 patients. For each sampled patient, we simulated a timeline akin to the real-world scenario (as shown in Fig. 1b). The baseline covariates such as demographics and medical history were measured at the time of hospitalization. We considered the first EA measurement as $t = 0$. After the initial measurement of EA, the patient was randomized into one of the four treatment arms for each drug, in addition to the standard of care as per the observed data. Simulated outcomes were measured at hospital discharge.

We compared pairwise outcomes for each treatment arm and computed the power of the analysis. Thus, varying the sample size and re-performing the analysis allowed us to identify the smallest sample needed to achieve a power of more than 80% for each treatment arm and outcome, with effect sizes as observed in our data, using a two-sided t -test.

Results

For both drugs of interest, Figure 2 shows the expected discharge outcomes (measured as binarized mRS) for each treatment arm estimated using the clinical trial

simulation. Differences in outcome across the arms were used to define the effect size. We estimated power curves for three combinations of treatment arms for both levetiracetam and propofol (see Figs. 3 and 4). We found that comparing levetiracetam or propofol to placebo yielded the maximum power for a given sample size, as opposed to comparing different treatment intensities. For levetiracetam, a sample size of at least 500 patients per treatment arm is needed to achieve power of more than 80%, whereas for propofol, at least 600 patients are needed per treatment arm. The need for large sample sizes can partially be attributed to the relatively small effects of these drugs on discharge outcome mRS. For levetiracetam, we found that a reduction of the drug dose from 15 to 7 mg/kg improves the outcome—this may be related to the potential negative side effects of a high drug dose. However, further reduction in levetiracetam dose from 7 to 3 mg/kg worsened outcomes, due to the impact of untreated higher EA burden. Interestingly, for propofol, we found no or minimal difference in outcomes between the highest (1 mg/kg/h) versus lowest dose (0.25 mg/kg/h) treatment arms. This could potentially be explained by the similar impact of propofol on EA at all three doses and that the highest propofol dose (1 mg/kg/h) used in this cohort was also a low dose leading to minimal side effects.

Discussion

Our findings demonstrate the strength of simulation-based design and power calculation for randomized trials of anti-seizure treatment of EA in acute brain injury. This work overcomes limitations of prior trials in the field by defining a data-driven null hypothesis and demonstrating the feasibility and practicality of varying trial designs. We propose our approach as a potential method to assist the design of future trials of anti-seizure treatment of EA in patients with acute brain injuries. The approach may enable high-powered and practical trials that have acceptable likelihood of producing clinically meaningful and applicable results.

The sample sizes determined by our simulations are significantly larger than those of prior trials examining EEG-guided anti-seizure treatments.^{13,17} A recent trial comparing suppression of EA for at least 48 h versus standard of care in patients with cardiac arrest and anoxic brain injury found no difference in neurologic outcomes.¹³ 172 subjects (84 per group) were included in the study. The sample size needed was determined based on an assumed prevalence of poor outcomes of 99% extrapolated from other external observational cohorts where poor outcome ranged from 90% to 100%.^{13,33,34} The investigators specifically aimed at a 7% lower

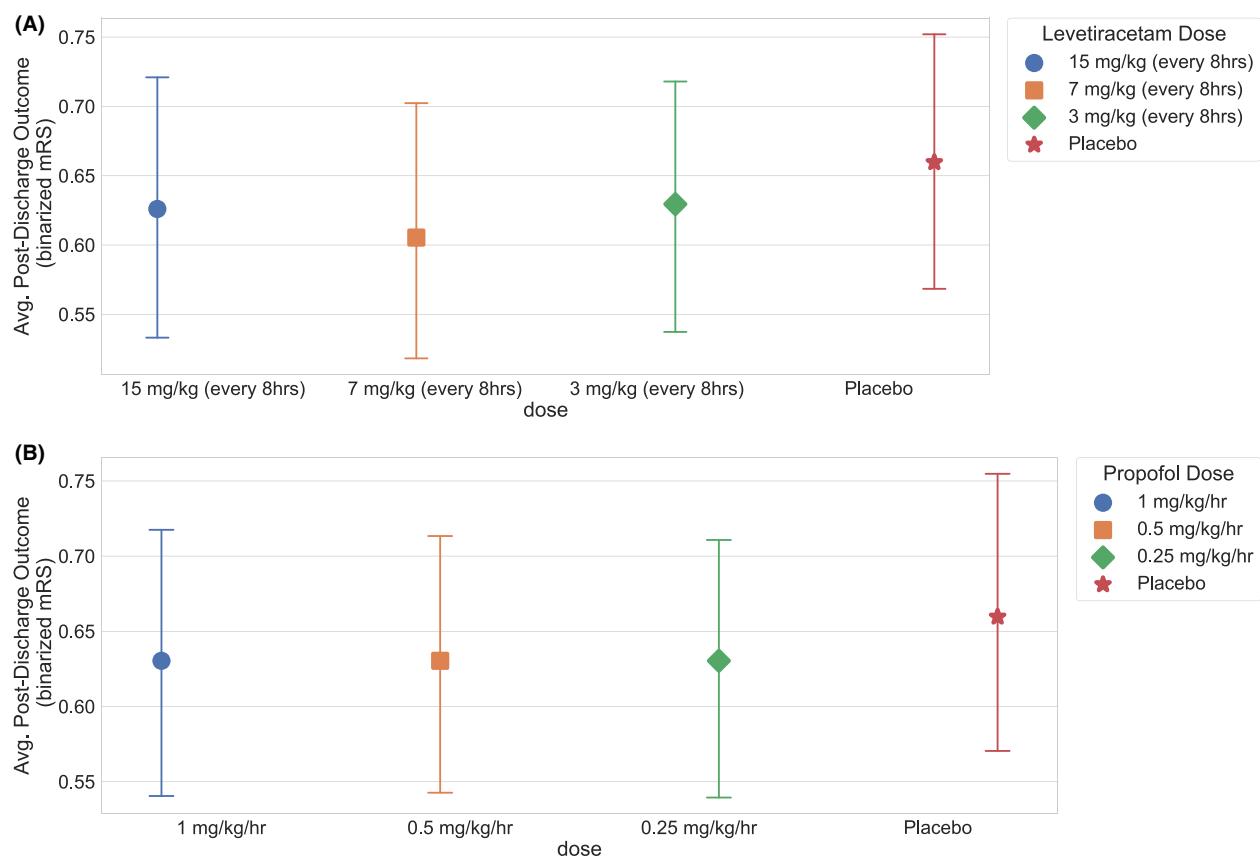


Figure 2. Expected post-discharge outcomes (binarized mRS) under each treatment arm for (A) levetiracetam and (B) propofol estimated using the observational data. The points show mean point estimate using the observational study and the error bars show standard error. The y-axis is the probability of poor outcome. mRS, modified Rankin Scale.

incidence of poor outcomes in the treatment group compared with the control group. This approach to power calculations did not protect them against possible misspecifications of the null (e.g., if 90% were used as the standard of care mortality and a 7% reduction were studied, then the standard difference in proportions power calculations would suggest sample sizes that are more than twice their original recommendations). Eventually, their observed data did not match the experimental null hypothesis: The observed proportion of poor outcomes was 90% in their treatment group and 92% in their control group. A second trial comparing lacosamide to phenytoin for the treatment of non-convulsive seizures enrolled only 37 subjects per arm for a non-inferiority trial.¹⁵ In the absence of efficacy data for anti-seizure medications, the sample size determination was based on consensus from investigators, by contrast to our data-driven methodology. A sample of 200 subjects was deemed as a feasible enrollment target, with power calculations performed for different potential response rates in both arms. The trial enrolled 74 subjects (37 per arm) before the withdrawal of funding.¹⁵ Generally, it appears

that these studies are underpowered to detect the effects they are interested in. Both studies come to a null conclusion that there is no evidence of a difference between the study arms. However, in light of the limitations in defining the null as detailed above, cautious interpretation is indicated for any clinical decision-making.^{35,36}

Using our PK/PD models, we included drug effectiveness in our simulations. Not surprisingly, trials comparing the drug to placebo required the smallest sample sizes, although these sample sizes were still significantly larger than prior trials. There is compelling evidence that EA can worsen outcomes,⁷ and therefore trials using a placebo are likely to be considered unethical. There remains significant uncertainty on the optimal treatment approach with multiple treatment strategies employed in current clinical practice ranging from monotherapy with low-dose ASM to combination therapy with high-dose ASMs and anesthetics.^{12,37} In our simulated trials, we considered a few of these treatment strategies and demonstrate that drug choice, dose, and effectiveness all strongly impact trial design. Further PK/PD modeling of other treatment approaches used in clinical practice is indicated to define

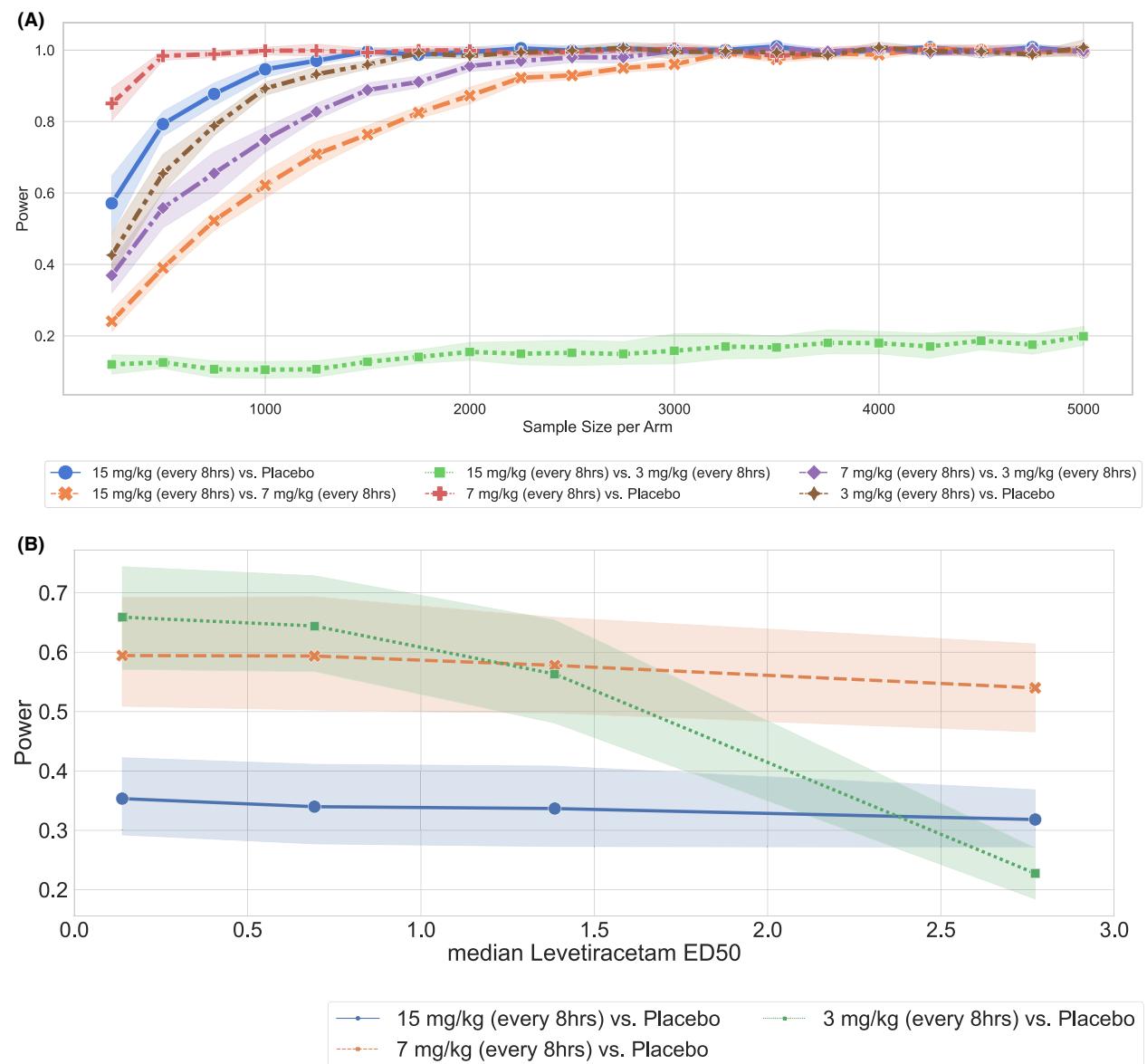


Figure 3. Power analysis and sample calculation for levetiracetam. (A) We estimate the sample size for 80% power calculated for binary combinations of treatment arms on binarized discharge mRS scores. (B) For a sample size of 100 units per treatment arm, we change the ED50 for levetiracetam to identify the drug-effect size at which the treatment effect is detected with 80% power on the discharge outcome. ED50, drug concentration necessary to reduce EA burden in a 10-min window by 50%; mRS, Modified Rankin Scale.

the full range of treatment responses and a reasonable null model.

A potential explanation for the small effect of anti-epileptiform treatment under our model is that these treatments alone may not be the most effective intervention for aSAH patients with EA. Recall that all patients in the simulation receive standard of care in terms of other treatments. The development of epileptiform activity in aSAH patients, particularly high-burden epileptiform activity, is also a harbinger of delayed cerebral ischemia

(DCI).³⁸ In addition, epileptiform activity is associated with increased cerebral metabolism, decreased brain tissue oxygenation, and secondary brain injury.²⁴ Therefore, a combination of ASM and/or anesthetic treatment with interventions geared toward increasing cerebral blood flow may need to be investigated in randomized trials of EEG-guided treatment in aSAH. Because functional outcomes are the result of multiple causes, it may also be appropriate and clinically relevant to investigate more proximal outcome measures comprised of EEG findings,

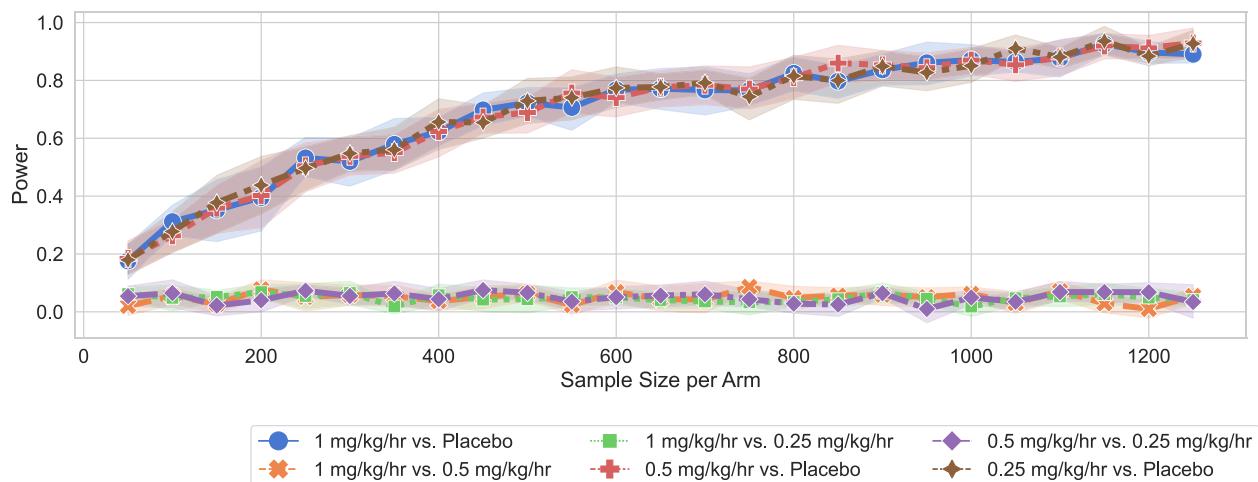


Figure 4. Power analysis and sample calculation for propofol. We estimate the sample size for 80% power calculated for binary combinations of treatment arms on binarized discharge mRS scores. mRS, modified Rankin Scale.

clinical examinations, and biomarkers of cerebral metabolism in this patient population.

There are several limitations to our study. First, the model for EEG simulations is based on data from a single-center, potentially limiting generalizability. We developed one-compartment PK/PD models from a relatively small cohort of patients, and studies are warranted to determine PK/PD and drug effectiveness for different ASMs and anesthetics in the aSAH population with varying disease severity. As Levetiracetam and propofol levels are not routinely or frequently measured in clinical practice, plasma concentrations were not included in our PK models. Our simulations include interventions geared toward increasing cerebral blood flow or metabolism only through standard of care, thus the effects of these interventions are not being directly investigated in our simulated randomized trials. We evaluated discharge functional outcomes, whereas greater effect sizes might be seen with more long-term outcomes (e.g., at 3, 6, or 12 months). Time to randomization in our simulations was restricted to a median of 24 h (the observed time to EEG initiation in our cohort), and we did not examine the impact of delays or longer time windows to randomization. Early intervention is relevant from a clinical standpoint given evidence that a higher epileptiform burden is associated with worse outcomes in acute brain injury patients.^{6,7} Finally, we combined all measured EAs into a single EA burden in our trial and did not distinguish between EA subtypes or EA frequencies. While ideally, each pattern type and higher frequencies should be investigated separately, in clinical practice these patterns are frequently overlapping, waxing or waning, or on a continuum. Isolating to a single pattern or frequency makes measuring a response to a treatment trial challenging. For

practical purposes, we binned all patterns together for this initial study. A future direction is to expand to individual pattern types and to analyze the dependence of the results on frequency. This will require additional methodological development, and an improved deep learning model to accurately quantify the frequency of rhythmic and periodic patterns. These need to be considered in future iterations of this work with larger observational datasets.

Conclusions

In conclusion, our simulated experiments using clinical observational data demonstrate that randomized trials of EEG-guided anti-seizure treatment may currently be infeasible. Further data is needed to define the natural course of epileptiform activity in a larger cohort of acute brain injury patients, describe the electrographic response of epileptiform activity to ASMs, and the appropriate therapeutic targets (e.g., EEG alone vs. EEG and biomarkers of metabolism). Further work is also indicated to determine which patient clinical profiles (disease type, severity, metabolism, and EA characteristics) are most likely to have an electrographic and clinical response to ASMs, and whether the response increases with a combination of therapeutic interventions (e.g., ASMs, low-dose anesthetics, and measures to augment perfusion). Identifying the right cohort, interventions, and outcomes are likely to increase the yield of such trials. Given the clinical complexity of acute brain injury (and in this case aSAH), the dynamic nature of the epileptiform activity, and the multifaceted pathophysiology of secondary brain injury, alternative trial designs with multi-tiered interventions are indicated to determine optimal treatment strategies for EA. Such trial designs also need to be considered for

other neurocritical care interventions. Importantly, these future studies fit within the simulation-based RCT paradigm developed in this work that combines modern statistical tools with biologically sound models.

Acknowledgment

None.

Author Contributions

Harsh Parikh contributed to conception and design of the study, analysis of data and drafting a significant portion of the manuscript and figures. Haoqi Sun PhD contributed to conception and design of the study, analysis of data and drafting the manuscript. Rajesh Amerineni contributed to acquisition and analysis of data and drafting the manuscript. Eric S. Rosenthal contributed to acquisition of data and drafting the manuscript. Alexander Volfovsky contributed to conception and design of the study, analysis of data and drafting the manuscript. Cynthia Rudin contributed to conception and design of the study and analysis of data and drafting the manuscript. M. Brandon Westover contributed to conception and design of the study, analysis of data drafting the manuscript. Sahar F. Zafar contributed to conception and design of the study, acquisition and analysis of data and drafting a significant portion of the manuscript and figures.

Funding Information

NIH K23NS114201 (SFZ), CAREER DMS-2046880 (AV), IIS-2147061 (HP, CR, AV), NIH R01NS102190, R01NS102574, R01NS107291 (MBW), R01DA056407 (HP).

Conflict of Interest

SFZ is a clinical neurophysiologist for Corticare and receives royalties from Springer for the publication of *Acute Neurology Survival Guide*, independent of this work. M Brandon Westover is a co-founder of Beacon Biosignals, independent of this work. All other authors report no conflict of interest.

Data Availability Statement

The data and software to reproduce these findings are available in a publicly accessible repository at bdsp.io.

References

1. Claassen J, Jetté N, Chum F, et al. Electrographic seizures and periodic discharges after intracerebral hemorrhage. *Neurology*. 2007;69(13):1356-1365.
2. Oddo M, Carrera E, Claassen J, Mayer SA, Hirsch LJ. Continuous electroencephalography in the medical intensive care unit. *Crit Care Med*. 2009;37(6):2051-2056.
3. Kurtz P, Gaspard N, Wahl AS, et al. Continuous electroencephalography in a surgical intensive care unit. *Intensive Care Med*. 2014;40(2):228-234.
4. Rodriguez Ruiz A, Vlachy J, Lee JW, et al. Association of periodic and rhythmic electroencephalographic patterns with seizures in critically ill patients. *JAMA Neurol*. 2017;74(2):181-188.
5. Zafar SF, Subramaniam T, Osman G, Herlopian A, Struck AF. Electrographic seizures and ictal-interictal continuum (IIC) patterns in critically ill patients. *Epilepsy Behav*. 2020;106:107037.
6. Zafar SF, Rosenthal ES, Jing J, et al. Automated annotation of epileptiform burden and its association with outcomes. *Ann Neurol*. 2021;90(2):300-311.
7. Parikh H, Hoffman K, Sun H, et al. Effects of epileptiform activity on discharge outcome in critically ill patients in the USA: a retrospective cross-sectional study. *Lancet Digit Health*. 2023;5:e495-e502.
8. De Marchis GM, Pugin D, Meyers E, et al. Seizure burden in subarachnoid hemorrhage associated with functional and cognitive outcome. *Neurology*. 2016;86(3):253-260.
9. Zafar SF, Postma EN, Biswal S, et al. Effect of epileptiform abnormality burden on neurologic outcome and antiepileptic drug management after subarachnoid hemorrhage. *Clin Neurophysiol*. 2018;129(11):2219-2227.
10. Zafar SF, Rosenthal ES, Postma EN, et al. Antiseizure medication treatment and outcomes in patients with subarachnoid hemorrhage undergoing continuous EEG monitoring. *Neurocrit Care*. 2022;36:857-867.
11. Sanches PR, Tabaeizadeh M, Moura LM, et al. Anti-seizure medication treatment and outcomes in acute ischemic stroke patients undergoing continuous EEG monitoring. *Neurol Sci*. 2022;43(9):5441-5449.
12. Amerineni R, Sun H, Lee H, et al. Using electronic health data to explore effectiveness of ICU EEG and anti-seizure treatment. *Ann Clin Transl Neurol*. 2021;8(12):2270-2279.
13. Ruijter BJ, Keijzer HM, Tjepkema-Cloostermans MC, et al. Treating rhythmic and periodic EEG patterns in comatose survivors of cardiac arrest. *N Engl J Med*. 2022;386(8):724-734.
14. Dhakar MB, Sheikh Z, Kumari P, et al. Epileptiform abnormalities in acute ischemic stroke: impact on clinical management and outcomes. *J Clin Neurophysiol*. 2022;39(6):446-452.
15. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the journal of clinical epidemiology. *J Clin Epidemiol*. 2011;64(4):380-382.
16. Stevenson NJ, Boylan GB, Hellström-Westas L, Vanhatalo S. Treatment trials for neonatal seizures: the effect of design on sample size. *PLoS One*. 2016;11(11):e0165693.

17. Husain AM, Lee JW, Kolls BJ, et al. Randomized trial of lacosamide versus fosphenytoin for nonconvulsive seizures. *Ann Neurol.* 2018;83(6):1174-1185.
18. Wilson DT, Hooper R, Brown J, Farrin AJ, Walwyn RE. Efficient and flexible simulation-based sample size determination for clinical trials with multiple design parameters. *Stat Methods Med Res.* 2021;30(3):799-815.
19. Arnold BF, Hogan DR, Colford JM, Hubbard AE. Simulation methods to estimate design power: an overview for applied research. *BMC Med Res Methodol.* 2011;11(1):94.
20. Huang C, Li P, Martin CR. Simplification or simulation: power calculation in clinical trials. *Contemp Clin Trials.* 2022;113:106663.
21. Hirsch LJ, Fong MW, Leitinger M, et al. American clinical neurophysiology Society's standardized critical care EEG terminology: 2021 version. *J Clin Neurophysiol.* 2021;38(1):1-29.
22. Struck AF, Westover MB, Hall LT, Deck GM, Cole AJ, Rosenthal ES. Metabolic correlates of the ictal-interictal continuum: FDG-PET during continuous EEG. *Neurocrit Care.* 2016;24(3):324-331. doi:[10.1007/s12028-016-0245](https://doi.org/10.1007/s12028-016-0245).
23. Vespa P, Tubi M, Claassen J, et al. Metabolic crisis occurs with seizures and periodic discharges after brain trauma. *Ann Neurol.* 2016;79(4):579-590. doi:[10.1002/ana.24606](https://doi.org/10.1002/ana.24606)
24. Witsch J, Frey HP, Schmidt JM, et al. Electroencephalographic periodic discharges and frequency-dependent brain tissue hypoxia in acute brain injury. *JAMA Neurol.* 2017;74(3):301-309. doi:[10.1001/jamaneurol.2016.5325](https://doi.org/10.1001/jamaneurol.2016.5325)
25. Vespa PM, O'Phelan K, Shah M, et al. Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. *Neurology.* 2003;60(9):1441-1446. doi:[10.1212/01.wnl.0000063316.47591.b4](https://doi.org/10.1212/01.wnl.0000063316.47591.b4)
26. Jing J, d'Angremont E, Zafar S, et al. Rapid annotation of seizures and interictal-ictal continuum EEG patterns. In 2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) 2018 (pp. 3394-3397). IEEE.
27. Ge W, Jing J, An S, et al. Deep active learning for interictal ictal injury continuum EEG patterns. *J Neurosci Methods.* 2021;351:108966.
28. Jing J, Ge W, Hong S, et al. Development of expert-level classification of seizures and rhythmic and periodic patterns during EEG interpretation. *Neurology.* 2023;100(17):e1750-e1762.
29. Talevi A, Bellera CL. One-Compartment Pharmacokinetic Model. *The ADME Encyclopedia: a Comprehensive Guide on Biopharmacy and Pharmacokinetics.* Springer Nature. 2021:1-8.
30. Felmlee MA, Morris ME, Mager DE. Mechanism-based pharmacodynamic modeling. *Methods Mol Biol.* 2012;929:583-600.
31. Goutelle S, Maurin M, Rougier F, et al. The Hill equation: a review of its capabilities in pharmacological modelling. *Fundam Clin Pharmacol.* 2008;22(6):633-648.
32. Chernozhukov V, Chetverikov D, Demirer M, et al. Double/debiased machine learning for treatment and structural parameters. *Econ J.* 2018;21(1):C1-C68.
33. Hofmeijer J, Tjepkema-Cloostermans MC, Blans MJ, Beishuizen A, van Putten MJ. Unstandardized treatment of electroencephalographic status epilepticus does not improve outcome of comatose patients after cardiac arrest. *Front Neurol.* 2014;31(5):39.
34. Cloostermans MC, van Meulen FB, Eertman CJ, Hom HW, van Putten MJ. Continuous electroencephalography monitoring for early prediction of neurological outcome in postanoxic patients after cardiac arrest: a prospective cohort study. *Crit Care Med.* 2012;40(10):2867-2875.
35. Lapalme-Remis S. A cry for survival? Rhythmic and periodic EEG discharges as treatment targets following cardiac arrest. *Epilepsy Curr.* 2022;22(5):294-296.
36. Wijdicks EF. Futility of suppressing seizure-like activity in postresuscitation coma. *N Engl J Med.* 2022;386(8):791-792.
37. Alvarez V, Ruiz AA, LaRoche S, et al. The use and yield of continuous EEG in critically ill patients: a comparative study of three centers. *Clin Neurophysiol.* 2017;128(4):570-578.
38. Kim JA, Zheng WL, Elmer J, et al. High epileptiform discharge burden predicts delayed cerebral ischemia after subarachnoid hemorrhage. *Clin Neurophysiol.* 2022;141:139-146.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Descriptive analysis and data summary of the cohort of patients in observational study.

Figure S1. Histogram of mean squared errors for predicting the EA burden over time compared with the observed EA burden. The MSE is measured for each patient in the observational study.

Figure S2. The ROC curve for the outcome prediction function.